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The reverse translation of a quantitative neuropsychiatric framework into preclinical studies: Focus on social interaction and behavior[☆]

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ABSTRACT

Following the Research Domain Criteria (RDoC) concept, major brain circuits are conserved in evolution and malfunctioning of a brain circuit will lead to specific behavioral symptoms. Reverse translation of patient-based findings from Alzheimer's disease (AD), schizophrenia (SZ) and major depression (MD) patients to preclinical models accordingly can be a starting point for developing a deeper understanding of the functional circuit biology and contribute to the validation of new hypotheses for therapeutic intervention in patients. In the context of the EU funded PRISM project, a preclinical test battery of tasks has been selected and aligned with the clinical test battery. It allows for assessment of social functioning, sensory processing, attention and working memory and is designed for validation of biological substrates from human molecular landscaping of social withdrawal. This review will broadly summarize the available literature on tasks for studying social behavior in rodents and outline the development of a preclinical test battery for the PRISM project by reverse translation.

The definition, assessment and neurobiology of social withdrawal, attention, memory deficits and sensory processing in AD, SZ and MD patients has been discussed in detail in other manuscripts of this issue. This review covers the reverse translation of these topics to preclinical models with a special focus on social interaction and behavior.

1. Reverse translation of social withdrawal into preclinical studies

Animal models of human diseases are based on known factors contributing to disease etiology or on risk factors contributing to quantifiable physiological or behavioral changes reflecting human disease states. Modelling psychiatric and neurological diseases, however, is hampered by multi-factorial, poorly understood disease etiologies and the complexity and heterogeneity of the human syndromes. One approach to address this issue is to focus on specific neuropsychiatric symptoms such as social withdrawal. Social withdrawal is a behavioral trait, which can be triggered in a species-specific manner by various genetic risk factors such as autism-related mutations or exposure to stressors.

Group-living of social species increases the individual survival rate and use of resources (Pusey and Packer, 1997). Flocking behavior in insects, fish or mammals is a prominent example of group behavior to decrease the individual predation risk by integrating into a large and

cohesive group. Computational models have been developed to describe the trajectories of individuals of large self-organized groups and to predict coordinated behavioral changes (Rosenthal et al., 2015). Similar algorithms also help to explain human collective behavior at mass gatherings such as demonstrations. Computational behavioral analysis of large groups of animals describes behavior at the levels of the whole swarm or school, but does not allow for behavioral analysis in individuals. To study social behavior of individuals, complexity needs to be reduced.

The size of social groups can range from pair-bonded units to large clusters and composition can vary in terms of gender ratio, age structure or the degree of relatedness. In mammals, social behaviors develop beginning with mother-child-relationship, continuing with juvenile play followed by gender-specific social behavior of adults (Wolf and Sherman, 2008). The net benefits of sociality exceed the costs, e.g. social support by familiar conspecifics is a powerful protective mechanism promoting stress resilience. At the same time, social stress by competition over access to food and mating opportunities can be costly for individuals (Blanchard et al., 2001a, 2001b). Social behavior in groups of wild mammals has been studied in a large variety of species including many rodent species. In their natural habitat, ground-living rodents typically live in burrow systems, however, domesticated laboratory rats and mice are typically housed in standard featureless cages supplied ad libitum food and water. In early attempts to analyze

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Table 1
Social behavioral ethogram of commonly used behavioral terms.

Behavior	Description	Literature
Type of social behavior: social investigation or friendly encounters		
approaching	One subject is moving towards another subject. Approaching usually ends in social contact.	(McFarlane et al., 2008)
contact	Two subjects being in close proximity to each other. Social contact can be further divided into nose-to-anogenital, nose-to-nose, nose-to head, nose-to-body and back-to-back contact	(de Chaumont et al., 2012; Defensor et al., 2011)
sniffing	One subject is sniffing another subject (or mutually sniffing). Sniffing can be further divided into nose-to-anogenital, nose-to-nose, nose-to-body sniffing	(Bolivar et al., 2007; de Moura Linck et al., 2008; File, 1980; McFarlane et al., 2008; Searce-Levie et al., 2008)
following	One subject is walking/running after another subject. Following usually ends in social contact. (Note: in aggressive context named “chasing”)	(Bolivar et al., 2007; de Moura Linck et al., 2008; File, 1980)
leaving	One subject is walking away from another subject (after or slightly before social contact).	(de Chaumont et al., 2012)
allo-grooming	One subject is licking and cleaning the fur of another subject	(Bolivar et al., 2007; de Moura Linck et al., 2008; File, 1980; McFarlane et al., 2008; Searce-Levie et al., 2008)
huddling	Subjects sleeping close together (usually in the home cage)	(Searce-Levie et al., 2008)
Type of social behavior: aggressive encounters		
tail rattling	Fast waving movements of the tail (usually against hard objects, e.g. cage wall) producing a rattling noise	(Searce-Levie et al., 2008)
chasing	One subject is running after another subject. Chasing usually ends in fighting.	(Bolivar et al., 2007; Searce-Levie et al., 2008)
mounting	One subject approaches another subject from behind, grabs with its forepaws, and exhibits rapid pelvic thrusting motions.	(Bolivar et al., 2007; de Moura Linck et al., 2008; File, 1980; Searce-Levie et al., 2008)
fighting	Two subjects showing a series of fast violent behaviors including kicking, biting, wrestling rolling over. Fighting usually elicit an aggressive or defensive posture.	(Bolivar et al., 2007; Searce-Levie et al., 2008)

rat behavior in a more naturalistic environment, large arenas filled with soil deep enough for burrowing have been introduced. However, these semi-natural environments were very labor-intensive and never became accepted (Blanchard and Blanchard, 2003).

In the following paragraphs the various aspects of social behavior will be discussed in more detail.

1.1. Modelling social behavior in the laboratory

Social behavior facilitates reproduction, helps to preserve and defend living space against intruders and enables access to certain food resources. To study social behavior and the underlying neuronal networks in the laboratory, rodent tests and models of reproductive (Dewsbury, 1981, 1984; Drickamer, 1974; Hull and Dominguez, 2007; Sutter et al., 2016), maternal (Barnett and Burn, 1967; Insel, 1997; Priestnall, 1973; Sherrod et al., 1974) and aggressive behavior (Dewsbury, 1984; Kuchiiwa and Kuchiiwa, 2014; Miczek et al., 2001; Thurmond, 1975) have been developed. More recently, also non-reproductive and non-aggressive social behavior of rodents has been studied in the context of central nervous system (CNS) disorders such as schizophrenia, depression or autism (Crawley, 2007a; Gururajan et al., 2010; Hanks et al., 2013; Miyakawa et al., 2003; Rincon-Cortes and Sullivan, 2016).

Social behavior is highly dynamic, species specific and influenced by genetic and environmental factors, which limits the direct translatability. For example, social organization of colonies of mice and rats differs and needs to be taken into account when interpreting and reverse translating social behavior of the experimental animals. Rats live in colonies made up of multiple social units (Lore and Flannelly, 1977) whereas mice live in breeding units, including the breeding pair and offspring (Benus et al., 1987). Social rank within the colony is important and influences social behavior since aggressive and non-aggressive mice react differently to environmental factors such as intruders (Benus et al., 1987).

In an experimental setting, numerous environmental factors such as housing conditions (Richter et al., 2010), handling and experimenter effects (Hurst and West, 2010; Schmitt and Hiemke, 1998) and other sources of stress (for review see Beery and Kaufer, 2015) can influence the behavior, including the social behavior, of the lab animals. As discussed below, automated tracking of the social behavior will greatly reduce influencing environmental factors.

1.2. Definition of social behavior

Social behavior is a broad term for activities involving at least two individuals of the same species (Sokolowski, 2010). We conducted literature research in PubMed and Scopus using different combinations of keywords such as “social behavior” or “social interaction” combined with “rodent” or “mice” or “rat”. The majority of scientific articles related to social behavior in rodents have operational definitions for social behavior rather than distinguishing between different forms of social behavior such as social approach, social contact, social follow etc. In the 1960’s and 70’s, about 50 different behaviors had been described in rodents using ethological techniques of observing naturally occurring behaviors in detail. This has been summarized in ethograms representing a sequence of measurable and frequently occurring postures (static) and events (involving movement) (Grant and Mackintosh, 1963; Grant, 1963; van Abeelen, 1964; Van Oortmerssen, 1971). However, some of the behavioral terms lacked precise definition and have been used interchangeably thereby contributing to the complexity of behavioral assessments (Van Oortmerssen, 1971). In a particular social context or environmental situation, e.g. introduction of a female or unfamiliar conspecific, some postures and events occurred more likely than others (van Abeelen, 1964). Based on these observations, social behavior interaction is distinguished from other forms of interactions with different motivational drives (Grant, 1963; Mackintosh, 1981) such as sexual behavior or agonistic behavior. In relation to human psychiatric disorders, the type of social behavior reflecting social encounters in a daily life situation is associated with nonaggressive, non-territorial and non-sexual behaviors and may be defined as “friendly encounters” in rodents. Nowadays, however, social behavior ethograms include only a small part of originally described terms. A brief summary of commonly described social behaviors is listed in Table 1.

Studying social behavior in a controlled laboratory environment and the growing field of behavioral genetics led to a change in the scope of behavioral observations from studying natural behaviors to measuring particular responses to specific stimuli. These responses might then be assigned to a behavioral function or motivational drive underlying the phenotype. In order to evaluate multiple behavioral functions or phenotypes potentially induced by genetic, pharmacological or environmental manipulation, behavioral test batteries are applied (Paylor et al., 2006; Powell and Miyakawa, 2006). For translational studies such as psychopharmacological drug tests these phenotyping assays require reliability, validity and replicability across laboratories (Crabbe et al., 1999; Wahlsten et al., 2003). Developing a

Table 2
Summary of social behavior tasks.

Name of the task	Paradigm	Resource
Social encounter/sociability/social preference/Social motivation		
<i>Social interaction test</i>	Reciprocal interactions (dyads) between two conspecifics. Preferably used in rats.	(File and Hyde, 1978; File and Seth, 2003; Kaidanovich-Beilin et al., 2011; Lee et al., 2005; Sams-Dodd, 1995, 1996)
<i>Three-chamber test</i> (<i>social preference, social approach, sociability test</i>)	Free choice between living and non-living stimulus. Preferably used in mice.	(Crawley, 2007a; Kaidanovich-Beilin et al., 2011; Moy et al., 2004; Nadler et al., 2004; Pearson et al., 2010; Yang et al., 2011)
<i>Social proximity test</i>	Two mice are placed simultaneously in a rectangular chamber for 10 min. Social contacts are manually scored in detail: Nose-to-nose, nose-to-head, nose-to-anogenitals, crawl over/under, upright, jumps.	Defensor et al., 2011
<i>Partition test</i>	Two animals placed in divided arena allowing olfactory and visual contact.	(Bronson and Eleftheriou, 1965; Kudryavtseva, 2003, 1994; Semple et al., 2012)
<i>Modified Y-maze</i>	Free choice between social and non-social arm.	(Bitanirhwie et al., 2010; Lai and Johnston, 2002; Toth and Neumann, 2013)
<i>Social preference-avoidance test</i>	Testing animal is first exposed to a non-social stimulus (in home cage or new environment) and then after a delay (or immediately see Lukas) the non-social stimulus is replaced by a social stimulus. Different paradigm for mice and rat exist. Usually used to measure social avoidance in socially defeated animals. Preference is shown when testing animal shows increased investigation toward social-stimulus.	(Berton et al., 2006; Lukas et al., 2011; Toth and Neumann, 2013)
<i>Social approach-avoidance test</i>	Testing arena consists of a two-compartment apparatus (small non-social and a larger compartment divided by a perforated wall). Testing animal is habituated to the small non-social compartment and is then allowed to explore the entire apparatus with a social stimulus in the larger compartment. Decreased time spent in social compartment represents social avoidance. Test designed for rats.	(Haller and Bakos, 2002)
<i>Social conditioned place preference</i> (<i>SCPP</i>) test <i>conditioned place preference for a social environment</i>	Animals were alternately housed socially and isolated for 24 h over 10 days. The conditioning context (social or isolate housing) was always counterbalanced relative to its pairing with the home cage environment (aspen or paper bedding). In the last session animals were allowed to freely explore a three-compartment arena including aspen, paper bedding and no bedding for a period of 30 min.	(Panksepp and Lahvis, 2007)
<i>Odour block test</i>	Discrimination between social odors: animal is presented with a wooden block scented with its own bedding and a block scented with another mouse's bedding.	(Fleming et al., 2008; Taylor et al., 2009, 2010; Tillerson et al., 2006)
Social recognition/social memory		
<i>Three-chamber-test</i> (<i>social recognition/partner preference test</i>)	Free choice between familiar and unfamiliar conspecific	(Crawley, 2007a; Kaidanovich-Beilin et al., 2011; Moy et al., 2004; Nadler et al., 2004; Pearson et al., 2010; Yang et al., 2011)
<i>Social habituation-dishabituation</i> (<i>social recognition</i>)	Repeated introduction of same social stimulus in the first four trials (= habituation to social stimulus reducing social interaction). In the 5 th trial, introduction of a novel stimulus animal (= dishabituation increasing social interaction)	(Choleris et al., 2003; Ferguson et al., 2002b; Millan and Bales, 2013; Tejada and Rissman, 2012; Winslow and Camacho, 1995)
<i>Social discrimination</i> (<i>social memory</i>)	In the first trial, test animal is first exposed to a stimulus animal. In the second trial (after delay), test animal is exposed to familiar stimulus animal (from 1 st trial) and a novel unfamiliar stimulus animal. Test animal should be able to discriminate between familiar and unfamiliar social stimuli by increasing the amount of anogenital investigation directed towards the novel stimulus animal.	(Engelmann et al., 2011, 1995; Ferguson et al., 2002b; Millan and Bales, 2013) Different version: (Arsenault et al., 2013; Thor and Holloway, 1982)
<i>SocioBox: social recognition paradigm</i>	SocioBox consists of a central open arena surrounded by five enclosures for social stimuli. Test animal is repeatedly placed in the center with five social stimuli animals. In the last trial, one of five stimulus animals is replaced by a new subject. Test animal should discriminate between familiar and new social stimuli.	(Krueger-Burg et al., 2016)
Aggressive/Territorial/ dominant behavior		
<i>Resident-intruder test</i>	Assessment of aggressive behavior by introducing an intruder mouse into the home cage of a resident mouse. Typically, the resident will attack the intruder to defend its territory.	(Ebert and Hyde, 1976; Heinrichs and Koob, 2006; Koolhaas et al., 2013; Mohn et al., 1999; Semple et al., 2012; Thurmond, 1975)
<i>Visible burrow system (VBS)</i>	Assessment of social and aggressive behaviours in a group of animals (usually rats) housed in a semi-natural environment.	(Arakawa et al., 2007; Blanchard et al., 1995; Blanchard et al., 2001a, 2001b; Pobbe et al., 2010; Wang et al., 2011)
<i>Food competition test</i>	Assessment of social competition between cage-mates for highly appetitive food pellet after food deprivation.	(Gellert and Sparber, 1979; Manosevitz, 1972; Merlot et al., 2004; Millard and Gentsch, 2006; Whishaw, 1988)
<i>Tube test</i>	Assessment of the social status by releasing two animals from the opposite ends in a narrow tube. After meeting in the middle, the submissive mouse will exit the tube by moving backwards (freely or forced by the dominant mouse).	(Benton et al., 1980; Kim et al., 2015; Lindzey et al., 1961; Miczek and Barry, 1975; Semple et al., 2012; Wang et al., 2011)
<i>Urinary marking patterns</i>	Using UV light to visualize urination patterns from two animals placed in a new environment. Typically, dominant mouse will mark the entire cage, while the submissive one is confined to the corner(s)	(Desjardins et al., 1973; Drickamer, 2001; Wang et al., 2011)
<i>Barbering = Whisker trimming or Dalila effect</i>	Dominant mice tend to remove whisker/and fur from submissive mice. Excessive barbering can be also associated with obsessive-compulsive behavior.	(Bresnahan et al., 1983; Garner et al., 2004; Kalueff et al., 2006; Long, 1972; Sarna et al., 2000; Strozik and Festing, 1981)

behavioral task complying with *trait* (interplay between genetic background and development incl. maternal care, housing conditions etc.), *state* (time of testing, experimenter skills, setup illumination etc.) and *technical factors* (data acquisition and analysis) is challenging (Hanell and Marklund, 2014; Sousa et al., 2006; Wahlsten et al., 2003).

1.3. Social behavioral tasks and paradigms

Various tasks for assessing different aspects of social behavior of mice and rats have been developed (Crawley, 2007a, 2007b; Defensor et al., 2011; File, 1980; Sams-Dodd, 1995; Silverman et al., 2010; Terranova and Laviola, 2005) and they are summarized in Table 2. In the *social interaction test* two unfamiliar rodents, mostly rats, are placed in a neutral environment and are allowed to interact freely. Initially developed to measure anxiety (File and Hyde, 1978; File and Seth, 2003), the *social interaction test* is used to measure reciprocal (dyadic) social interactions indicating motivation for social encounters (Lee et al., 2005; Qiao et al., 2001; Sams-Dodd, 1995, 1996). In mice, the *three-chamber test* is the most commonly applied social behavior test for assessment of sociability and social approach (Crawley, 2007a; Moy et al., 2004; Nadler et al., 2004). In the *three-chamber test*, the test subject freely can explore the apparatus, which includes social stimuli (unfamiliar mouse in enclosure) and non-social stimuli (empty enclosure). Moreover, the *three-chamber test* also can be used to assess social memory by introducing familiar and non-familiar social stimuli (Nadler et al., 2004). Preventing direct physical contacts between test subject and stimulus mouse, the *three-chamber test* allows for higher experimental control by reducing confounding agonistic behaviors and simple objective scoring (Nadler et al., 2004) as compared to the *social interaction test*. However, translational validity of the *three-chamber test* has been criticized given the fact that measuring social approach behavior might not be the basis of social impairment in human mental disorders related to complex behavioral abnormalities involving further actions (postures, events). In the *social proximity test*, for example, social encounters such as nose-to-nose or nose-to-head interactions among two conspecifics have been observed (Defensor et al., 2011). Considering the orientation of social interactions, Defensor et al. could show that BTBR mice avoid reciprocal frontal orientations, which draw analogies to gaze aversion (reduced direct eye contact) associated with autism (Defensor et al., 2011). Alternative tests assessing sociability and social approach include *modified Y-Maze* (Bitanirwe et al., 2010; Lai and Johnston, 2002; Toth and Neumann, 2013) and *partition test* (Bronson and Eleftheriou, 1965; Kudryavtseva, 2003; Semple et al., 2012) that mainly differ in the apparatus design. *Social preference-avoidance test* (Berton et al., 2006; Lukas et al., 2011; Toth and Neumann, 2013) and *social-approach-avoidance test* (Haller and Bakos, 2002) have originally been described to measure social approach-avoidance behavior in defeated animals spending significantly less time in close proximity to social stimuli (Berton et al., 2006; Dadoimo et al., 2011; Hollis and Kabbaj, 2014).

Social recognition and social memory formation in rodents facilitates kin recognition and hierarchy establishment using different modalities including olfactory, pheromonal, visual and auditory cues. In humans, social perception deficits, such as disrupted face identity recognition and facial expression perception have been reported in autism disorder (Schultz, 2005). Social recognition and memory in rodent models can be assessed by a number of paradigms including the *three-chamber test* (see above), *social habituation-dishabituation* (Choleris et al., 2003; Ferguson et al., 2002a; Millan and Bales, 2013; Winslow and Camacho, 1995) *social discrimination* (Engelmann et al., 2011, 1995; Ferguson et al., 2002b; Millan and Bales, 2013) and *SocioBox* (Krueger-Burg et al., 2016). In the *social habituation-dishabituation paradigm*, a test subject is exposed to the same social stimulus over several consecutive trials (habituation). In the final trial, the subject is presented with a novel stimulus animal (dishabituation). In the *social discrimination paradigm*, a subject animal is first presented to one social

stimulus and in the second trial, the subject animal is exposed to both, the familiar and a novel stimulus animal. *SocioBox* consists of a central open arena surrounded by five enclosures for social stimuli (Krueger-Burg et al., 2016). Test animal is repeatedly placed in the center with five social stimuli animals. In the final trial, a novel (unfamiliar) mouse replaces one of the stimulus animals. Test animal should discriminate between familiar and new social stimuli.

As discussed above, aggressive and dominant behaviors are part of the social behavior repertoire of rodent species and can be assessed using a variety of paradigms. Aggressive behavior is mainly studied in the *resident-intruder* paradigm by introducing an unfamiliar intruder mouse to the home cage of a resident mouse (Ebert and Hyde, 1976; Heinrichs and Koob, 2006; Koolhaas et al., 2013; Mohn et al., 1999; Semple et al., 2012; Thurmond, 1975). The resident will defend its territory by attacking the intruder, who will show defensive behavior.

The *visible burrow system (VBS)* has originally been described as paradigm to study offensive and defensive behaviors in mixed-sex groups of rats housed in semi-natural environment (Blanchard and Blanchard, 1989; Blanchard et al., 2001a, 2001b). Since then, it has widely been used in different rodent species to measure different aspects of defense behavior and social status within a group (Arakawa et al., 2007; Blanchard et al., 1995, 2001a, 2001b; Pobbe et al., 2010; Wang et al., 2011).

The social status is a crucial factor influencing the social behavior of an individual within a group (see below). Social status can be assessed by observing dominant and aggressive behaviors such as competitive behavior in the *food competition test* (Gellert and Sparber, 1979; Manosevitz, 1972; Merlot et al., 2004; Millard and Gentsch, 2006; Whishaw, 1988), wide-spread *urinary marking* by the dominant animal (Desjardins et al., 1973; Drickamer, 2001; Wang et al., 2011) and *barbering* (Bresnahan et al., 1983; Garner et al., 2004; Kalueff et al., 2006; Long, 1972; Sarna et al., 2000; Strozik and Festing, 1981). A simple and robust test to assess dominant behavior is the *tube test* declaring a subject as dominant when the conspecific (submissive) is forced to move backwards in a narrow tube (Benton et al., 1980; Kim et al., 2015; Lindzey et al., 1961; Miczek and Barry, 1975; Semple et al., 2012; Wang et al., 2011).

1.4. Bringing natural behavior to the laboratory; the social environment

An environment that imitates the natural situation triggers a broader range of behaviors in laboratory animals and thereby increases the sensitivity for detecting specific behaviors. The environment of the animal can be differentiated between the social and the non-social environment. The effects of environmental enrichment are diverse and complex, and increase variation within strain and between strains (Abramov et al., 2008). Different laboratories using the same experimental setting can already produce quite dissimilar results and enrichment may have altered results depending on the characteristics of the animal (for review see Toth, 2015 and Toth et al., 2011). Surely, certain enrichments are a necessity to display particular behaviors. Nest building, for example, is not possible without nesting material. However, from all possible enrichments none has the impact of the introduction of a conspecific. Going from single housing to group housing increases the behavioral repertoire significantly, as it opens up the possibility to display social behavior. When trying to elucidate social group dynamics and its resulting behavior, many underlying processes have to be considered. Social interactions have direct and indirect consequences. Not only the interaction itself, but also the hierarchical position of the animal has its effects. Social status (i.e. hierarchy) is part of the daily lives of all social animals, including humans. The position as either a dominant or a subordinate individual affects behavior and physiology. Thus, the effects of the social environment cannot be disregarded when studying behavior or physiology. It will most certainly affect experimental outcomes.

The establishment and maintenance of social interaction and social

bonds is crucial for survival of every social species. From an ultimate perspective, cooperation and pair bonding can benefit the persistence of the species. However, social behavior also has its more proximate outcomes. Social interactions have direct consequences for the individual outside of the social domain, both physiological and behavioral. Morrison and Hill (1967) showed that rats were less fearful when tested in groups of three (Morrison and Hill, 1967). This effect appeared to be strongest when animals were reared in groups as well. The effect was suggested as being some sort of (learned) reassurance (Morrison and Hill, 1967). Rats do not only show less of a fear response when there are companions in their vicinity, they also actively seek them when they are frightened (Taylor, 1981). The phenomenon in which social interaction ameliorates fear/stress is referred to as social buffering (for review see (Kikusui et al., 2006)). It is suggested that social buffering is mediated by the olfactory system via the connection between the posteromedial region of the olfactory peduncle (pmOP) and the lateral amygdala (LA) (Kiyokawa et al., 2012). Indeed, a correlation between neuronal responses in the LA and freezing duration with and without conspecifics has been found in rats (Fuzzo et al., 2015). Social buffering of fear responses is not confined to rodents. Humans appear to show similar reactions when exposed to fearful stimuli. A companion ameliorates fear (Friedman, 1981) and people affiliate more during a fearful situation (Morris et al., 1976). The amelioration of fear/stress by social interaction affects physiology directly as well. Wound healing and stroke outcome are both ameliorated by social interaction in social species. Presumably, this effect is mediated by oxytocin, leading to lowered blood glucocorticoid levels (for review see (DeVries et al., 2007)).

As social interaction is adaptive, it does not come as a surprise that it is reinforced. In humans, social relationships are essential components of well-being and health (see for review (Krach et al., 2010)). And animal studies have previously shown that social behavior in itself can be rewarding (see for review (Trezza et al., 2011)). This is exemplified by the use of the social conditioned place preference test, in which a social animal displays a preference for environmental cues coupled to being housed with cage-mates versus being single-housed (Dölen et al., 2013).

Social interactions cannot only decrease stress levels, they can also increase them. When an animal is exposed to an aggressive defeat, it experiences a substantial amount of stress, as measured by an increase in heart rate, corticosterone and testosterone. This phenomenon has been coined “social defeat stress” (Koolhaas et al., 1997). Social defeat stress is a translatable and physiological stressor, which plays an important role in colonies of rodents.

Group housing of animals introduces the establishment of a social hierarchy, as animals now have to compete over resources and space. The social status of an animal has multiple consequences for the individual, both in behavior and physiology. Dominant animals, by definition, display more aggressive behavior (e.g. biting and chasing), versus the subordinates, which show more defensive behavior (e.g. fleeing and submissive postures) (Blanchard et al., 1995; Horii et al., 2017). Their dominance status also affects behavior of the other animals; subordinates display more anxiety related behavior. Longer durations of immobility in the forced swim test can also be observed, which is often referred to as depressive-like behavior (Horii et al., 2017). In semi-natural environments, dominant animals spend more time in the open areas of the environment. On the contrary, subordinates appear to be inhibited in movement. Furthermore, fewer drinking and eating episodes can be observed in subordinates and they display less sexual behavior (for review see (Blanchard et al., 1995)). However, the effects of the social hierarchy reach beyond behavior and also lead to clear physiological consequences. One of the first physiological effects that was elucidated is its effect on body weight. Body weight is differentially affected in dominant and subordinate animals. While the former appears to either have an increase in body weight, the latter seems to experience either less gains or even a drop in body

weight (Tamashiro et al., 2004). This falls in line with the observed differences in feeding behavior, as the subordinates feed less. Pain perception is also shown to differentiate between dominants and subordinates. Aghajani et al. (2013) injected dyads of dominant and submissive animals with formalin and determined the acute (0–6 min post-injection) and late (15–60 min post-injection) nociceptive response. While subordinate mice showed a higher pain response in the acute phase, they also had a lowered nociceptive score during the late phase (Aghajani et al., 2013).

Next to these directly observable consequences of subordination, the social status of an animal also affects its (neuro)endocrine system. Testosterone levels are affected, as they are lowered in subordinates (Blanchard et al., 1995; Tamashiro et al., 2004), which is combined with a reduction in testes weight (Blanchard et al., 1995). However, this interaction between testosterone levels and social status appears to be only valid for colonies that exhibit a highly despotic hierarchy (Williamson et al., 2017). In low despotism groups and dyads of mice, no relation can be found between testosterone and status (Williamson et al., 2017). The opposite relation can be found regarding social status and (basal) corticosterone (CORT), subordinate rats showed elevated plasma CORT levels (Tamashiro et al., 2004). Williamson et al. (2017) show the same trend in mice, though this is only observed in groups of high despotism (Williamson et al., 2017). The relationship between CORT and status may be confined to colony based subordination as dyadic dominant/subordinate animals both show elevated CORT levels (Aghajani et al., 2013) or even the opposite effect, high CORT in dominant animals (Williamson et al., 2017). Together, this suggests that the stability of the hierarchy modulates the neuroendocrine effects of social status. In other words, its effects are influenced by how certain an individual is of its rank. Knight and Mehta (2017) studied the effect of hierarchy stability on stress in humans and show comparable results. Cortisol reactivity to a stressor was influenced by the interaction between status and stability. High status individuals show blunted CORT reactivity in a stable hierarchy but display an increased CORT response when they could potentially drop in status (i.e. an unstable hierarchy). This coincided with the subjects' perceived control of status. High status individuals felt more in control in a stable hierarchy, when compared to individuals with a low social status. However, in an unstable hierarchy the level of subjective control was indistinguishable (Knight and Mehta, 2017). The human situation of high or low control over status could be compared to a rodent hierarchy of high or low despotism. Both indicate a possible lack of control for the subject and, thus, the stability of the hierarchy. Combined, these results indicate an effect of status on stress, modulated by the stability of the hierarchy (i.e. the control of the individual).

Social status also seems to be related to the immunological responsiveness of individuals. In dyads of mice, subordinates had elevated serum levels of proinflammatory cytokines (i.e. IL-6 and IL-1 β) when compared to dominant animals (Aghajani et al., 2013). Interestingly, elevated levels of IL-6 in response to a stressor can be found in humans with a low subjective social status compared to those who perceive their social status as high (Muscatell et al., 2016). A correlation between status and (hypothalamic) IL-1 levels was also found in rats, where submissive rats had higher IL-1 levels. However, the same study did not find a correlation between plasma CORT and hypothalamic IL-1 concentration (Barnum et al., 2008). As such, it is clear that social status influences the immune response, but the mechanism remains to be elucidated.

In addition to its peripheral effects, the hierarchy also affects the brain. Social status influences Corticotropin-releasing factor (CRF) in the amygdala, with higher social status being linked to higher CRF mRNA levels. Likewise, relative hippocampal glucocorticoid receptor (GR) and brain-derived neurotrophic factor (BDNF) expression are elevated in socially dominant animals (So et al., 2015). The reward system is also affected by rank. Dominant rats show higher dopamine transporter (DAT) and lower dopamine content in the nucleus

accumbens shell. Furthermore, Dopamine receptor D2/3 binding was found to be elevated in the accumbens shell and in the dorsal striatum (Jupp et al., 2016). Interestingly, this coincides with increased rates of self-administration of a highly rewarding substance, cocaine (Jupp et al., 2016).

Social interactions are shown to similarly lead to direct physiological and behavioral consequences both in humans and in animals. Social interaction influences anxiety, stress and rewards both in humans and in rodents. As such, it is an excellent target for translational research. Social status modulates the consequences of social interactions, for example by determining if a confrontation is experienced as a win or loss. The hierarchical position of the animal has implications outside of these social interactions. Social status influences body weight, immune function, stress reactivity and, possibly, reward sensitivity. With this wide variety in physiological effects it is clear that the social environment has a great impact on the animal and thus on experimental outcomes.

1.5. Taking away the social environment; Social isolation

Isolating an individual from its social environment deprives an animal of a “normal” environment. Indeed, guidelines for animal caretaking advise researchers that the housing of the animal should account for its social needs unless needed for the sake of the experiment (National Research Council (U.S.). Committee for the Update of the Guide for the Care and Use of Laboratory Animals and Institute for Laboratory Animal Research (U.S.), 2011). Depriving an animal of its social environment can alter its behavior. Effects can be seen on hyperactivity (Bianchi et al., 2006; Bickerdike et al., 1993; Vöikar et al., 2005; Zhao et al., 2009), learning (Bianchi et al., 2006; Vöikar et al., 2005), aggression (Koike et al., 2009; Miczek and O'Donnell, 1978; Wongwitdech and Marsden, 1996; Zhao et al., 2009), social behavior (Hol et al., 1999; Zhao et al., 2009) and (inconsistently) anxiety (Fone et al., 1996; Vöikar et al., 2005). Furthermore, a recent meta-analysis by Schipper et al. (2018) indicated that social isolation increased food intake and visceral white adipose tissue, with a suggestion that the highest effect of isolation can be found during adolescence (Schipper et al., 2018). Indeed, the effects of social isolation are dependent on the stage of life in which the animal is deprived of the social environment (e.g. Arakawa, 2003; for review see Hall, 1998). Adolescence appears to be a critical time window in the effects of social isolation, leading to effects not seen when animals are isolated during other life stages (Arakawa, 2003; Einon and Morgan, 1977). Isolating rodents during adolescence induces impaired social recognition (Kercmar et al., 2011; Zhao et al., 2009), reduced social interaction (Lukkes et al., 2009), and schizophrenia-like symptoms such as reduced prepulse inhibition and hyperactivity (Day-Wilson et al., 2006; Fone and Porkess, 2008; Heidbreder et al., 2000). However, social isolation has little impact on AD-like symptoms in the triple transgenic mouse model of AD (3xTg-AD), a line with a genetic predisposition for AD (Pietropaolo et al., 2009). Together, this suggests social isolation as a potent tool for modelling symptoms of multiple neuropsychiatric disorders. The isolation of rodents leads to symptoms comparable to those seen in depression and schizophrenia, and as such might have great translational value. Indeed, in human, social isolation is suggested to cause significant effects. Both in adolescents (Witvliet et al., 2010) and adults (Ge et al., 2017) social isolation has been connected to depressive symptoms. Comparable to rodents, an adverse social environment of adolescents increases the chance of having a neuropsychiatric disorder in adulthood (McLaughlin et al., 2010). Children and adolescents (i.e. 4–16 years of age) showing internalizing behaviors, such as being socially withdrawn, show a greater incidence of mood disorders such as major depressive disorder (Roza et al., 2003). Interestingly, social withdrawal is a symptom of multiple neuropsychiatric disorders (American Psychiatric Association, 2013). And often this symptom precedes the onset of the disorder itself, as can be seen in for example in

Schizophrenia (Dominguez et al., 2010) and Alzheimer's disease (Delrieu et al., 2015; Feldman et al., 2004). However, it is currently unclear whether social withdrawal is a symptom or a cause, and whether this is the same for these diseases. As the social isolation of rodents models a socially withdrawn state, it provides a promising method for further elucidating the mechanisms leading to neuropsychiatric disorders. As the age of the animal during isolation appears to be a key factor in the displayed phenotype, this might shed light on the origin of the disease phenotype in humans. For example, a depressive-like phenotype can be found after social isolation in the third postnatal week (Lo Iacono et al., 2015) and adolescent isolation gives rise to schizophrenia-like symptoms (Fone and Porkess, 2008). As such, depriving an animal of its social needs appears to be a powerful tool in translational research, with seemingly considerable construct and face validity. However, there are still challenges in connecting the phenotype produced by social isolation to human neuropsychiatric disorders.

1.6. Analysis of social behavior

As described above, social behavior paradigms measure particular aspects of social behavior, such as social preference, social memory or social rank. By reducing complexity of the observed behavior, specific social interaction of two animals can be evaluated in a reproducible, quantitative manner. This allows for studying the influence of genetic or pharmacological manipulations on those behaviors. However, only a small part of the repertoire of social behavior is evaluated in each test. In order to increase the value of translational research, the complexity of a behavior task needs to be increased without decreasing reproducibility and losing the potential for quantitative assessment. Conventionally, rodent behavior is scored manually by looking in detail at animals' activities, such as postures and movements in or without presence of conspecifics, and as a result building behavioral ethograms (Grant and Mackintosh, 1963; van Abeelen, 1964; Van Oortmerssen, 1971). Manual observation, however, is time-consuming, labor-intensive and requires long training. Furthermore, it is limited by human performance, which restricts the number of behaviors observed in the ethograms. For human observers it is easier to detect behaviors appearing frequently than those occurring sporadically. Further limitations comprise experimenter bias by subjective assessment and/or the lack of definitions of behavioral terms as described above (Van Oortmerssen, 1971).

1.7. Automatic behavior analysis

Considering recent progress in sensor technologies and video analysis and its impact on daily life, manual scoring of mouse behavior in a standard laboratory environment seems inefficient and overcome. However, for reproducible quantification, the respective behavior precisely needs to be defined. As described above, definition of social behaviors is an issue and poorly defined behavior will lead to large variation. On the other hand, a too close definition will also limit the value of automatic behavior analysis and leads to oversimplified behavioral ethograms.

Automation can overcome some limitations of human observation, however, computerized tracking systems use different algorithms to detect and define behavior. Human observers can better determine behavioral events while computers perform more reliable in fast locomotion tracking. Automatic scoring of behavior needs to be well aligned with manual scoring and scoring parameters need to be adjusted flexibly while teaching the computerized system.

Translational social behavior research will profit most from automatic behavior analysis if complex behaviors of individual animals in a group of mice can be monitored continuously during dark and light phases without visibly labelling the animals or other environmental influences.

Automatic tracking systems, which fulfil those criteria, are currently

Table 3
Tracking systems for mouse behavior.

Tracking system	Benefits	Limitations	Literature
The Observer XT (Noldus Information Technology) Video-based software for manual behavioral scoring	<ul style="list-style-type: none"> Flexible definition of behaviors re-analysis and frame-by-frame analysis available unlimited number of animals (in theory) home cage or any other environment 	<ul style="list-style-type: none"> number of tracking events limited by human observer capacity confounded by human error suitable for short-term analysis 	(Noldus, 1991)
EthoVision® (Noldus Information Technology) Automated video tracking software for home-cage-like observations (PhenoTyper).	<ul style="list-style-type: none"> automatic long-term monitoring 	<ul style="list-style-type: none"> Color marking required (fur colored) Not more than 2 animals 	(de Visser et al., 2006; Sams-Dodd, 1995; Spink et al., 2001)
VMB Tracking System Based on infra-red pulses communicating with transponders fixed on animal's head. 3D location calculated by triangulation.	<ul style="list-style-type: none"> Tracking independent of lighting condition Larger spatial resolution ($\pm 0,1$ mm under optimal conditions) compared to photobeams Group size of 8 animals group of 3 mice automatic home cage monitoring no animal marking required (combination of blob and contour tracking algorithm) 	<ul style="list-style-type: none"> transponder size and weight could influence animal's behavior System is sensitive to IR noise produced by sunlight, lamps, heaters, non-homogenous room temperature... 	(Vatine et al., 1998)
Smart Vivarium Video tracking algorithm for home cage monitoring (side view)	<ul style="list-style-type: none"> validated, long reference list automatic no experimenter influence long-term monitoring home cage like environment high-throughput testing (max.16 animals) flexibility in task design up to 128 subjects tracked long-term tracking automatic home cage environment 	<ul style="list-style-type: none"> limited literature available no data on social behavior available 	(Belongie et al., 2005)
IntelliCage (NewBehavior AG) RFID-based apparatus	<ul style="list-style-type: none"> validated, long reference list automatic no experimenter influence long-term monitoring home cage like environment high-throughput testing (max.16 animals) flexibility in task design up to 128 subjects tracked long-term tracking automatic home cage environment 	<ul style="list-style-type: none"> Not suitable for monitoring social behavior, rather for spontaneous and learning behavior 	(Endo et al., 2011; Galsworthy et al., 2005; Rudenko et al., 2009; Vannoni et al., 2014))
PhenoMaster/LabMaster (TSE Systems, Germany) Based on infrared light beams (ActiMot)	<ul style="list-style-type: none"> Semi-natural environment (4,5 m²) Long-term monitoring 24/7 group of up to 40 mice No marking required automatic 	<ul style="list-style-type: none"> limited information about complex behaviors, like social interactions 	(Bode et al., 2008; Urbach et al., 2014)
RFID-based tracking system in semi-naturalistic enclosure (SNE)	<ul style="list-style-type: none"> Semi-natural environment (4,5 m²) Long-term monitoring 24/7 group of up to 40 mice No marking required automatic 	<ul style="list-style-type: none"> no information given on complex behaviors like social interactions, rather for locomotion 	(Lewejohann et al., 2009)
MiceProfiler Video tracking combined with geometrical primitives	<ul style="list-style-type: none"> Long-term tracking (24 h) Complex cage environment 	<ul style="list-style-type: none"> established for 2 mice ID overlaps have to be corrected manually 	(de Chaumont et al., 2012)
RFID-based tracking system integrated into a multi-compartment behavioral testing apparatus (BTA)	<ul style="list-style-type: none"> Long-term tracking (24 h) Complex cage environment 	<ul style="list-style-type: none"> Established for 2 mice (more possible?) information limited to animal's position in distinct location (no information about what behaviors occur in the location) color marking 	(Howerton et al., 2012)
Automatic video tracking system for detecting multiple animals using different fluorescent colors for identification.	<ul style="list-style-type: none"> automatic groups of 4 mice semi-natural environment long-term tracking over day and night 	<ul style="list-style-type: none"> color marking 	(Shemesh et al., 2013)
Tracking system combining RFID signal and video tracking.	<ul style="list-style-type: none"> Group-housed mice long-term tracking automated social behavior phenotyping semi-natural environment 	<ul style="list-style-type: none"> commercially not available 	(Weissbrod et al., 2013)
DuoMouse Video tracking combined with machine learning (hidden Markov model, HMM)	<ul style="list-style-type: none"> automatic established for detection of social behavior large-scale analysis group of 4 mice tested (up to 20 animals possible depending on the species) no marking required fully automated re-identification of animals when they temporarily disappear from view or across videos 	<ul style="list-style-type: none"> not more than 2 animals w/o ID differentiation well-trained human observer required for training of the HMM 	(Arakawa et al., 2014)
idTracker Video-based tracking algorithm extracting fingerprint/signature of unmarked individuals	<ul style="list-style-type: none"> group of 4 mice tested (up to 20 animals possible depending on the species) no marking required fully automated re-identification of animals when they temporarily disappear from view or across videos 	<ul style="list-style-type: none"> readout: trajectories limited data in mice (mainly fish) 	(Perez-Escudero et al., 2014)
PhenoCube (PsychoGenics) Based on hardware modifications of Intellicage units	<ul style="list-style-type: none"> Group-housed mice long-term tracking (data obtained every second for 24 h over several days) tacking of dynamic interaction due to depth sensing 	<ul style="list-style-type: none"> artificial arena (no environmental cues) 	(Alexandrov et al., 2015)
	<ul style="list-style-type: none"> Not more than 2 animals animal of different coat colour required 		(Hong et al., 2015)

(continued on next page)

Table 3 (continued)

Tracking system	Benefits	Limitations	Literature
Automatic tracking system combining depth sensing, video tracking, and machine learning	<ul style="list-style-type: none"> • 3D tracking • Home cage environment (though w/o houses/igloos) 		
RFID-based (in UHF band) tracking system for long-term monitoring of groups of mice	<ul style="list-style-type: none"> • UHF bandwidth (860–960 MHz) allows multiple and simultaneous tag reading • Identification of individual mice within a group (due to unique RFID chip ID) • Long-term tracking • 3D reconstruction of mice movement 	<ul style="list-style-type: none"> • Detection of behavioral events limited to the evaluation of the RFID tag's proximity to the antennae • Established for 2 mice (more possible?) 	(Catarinucci et al., 2014; Macri et al., 2015)
Behavioral Observation Research Interactive Software (BORIS) Video-based software for manual behavioral scoring	<ul style="list-style-type: none"> • Flexible definition of behaviors • re-analysis and frame-by-frame analysis available • unlimited number of animals (in theory) • can be applied in the home cage/any environment 	<ul style="list-style-type: none"> • number of tracking events limited by human observer capacity • confounded by human error • suitable for short-term analysis 	(Friard and Gamba, 2016)
Home Cage Analysis (HCA) system (Actual Analytics Ltd, UK), RFID-based automated long-term monitoring of group housed mice	<ul style="list-style-type: none"> • No experimenter interference • No environmental perturbations since tacking in home cage • Long-term tracking → 7 days • Groups of 3 mice/cage 	<ul style="list-style-type: none"> • under-report of distance moved due to low spatial resolution (19–50 mm) • when moving quickly animal can be entirely missed • each antenna can read a single chip (presumably the strongest signal) per cycle, when 2 animals within 50 mm reading range, only one is detected 	(Bains et al., 2016)
Eco-HAB RFID-based tracking in a four-compartment apparatus	<ul style="list-style-type: none"> • long-term tracking (72 h) • cohorts of up to 12 mice • semi-natural habitat 	<ul style="list-style-type: none"> • reports only location of an animal → limited information about behaviors occurring at the location 	(Puścian et al., 2016)
RFID-assisted SocialScan Integration of RFID and video tracking	<ul style="list-style-type: none"> • Group-housed mice • long-term tracking • automated • social behavior phenotyping • semi-natural environment 		Peleh et al. (Manuscript in preparation)

not (commercially) available, and/or are restricted by one or several limitations: single-animal assay (Aguilar et al., 2007; Aragão et al., 2011; Casadesus et al., 2001; Crispim Junior et al., 2012; Goulding et al., 2008; Jhuang et al., 2010; Krueger-Burg et al., 2016; Quinn et al., 2006; Solberg et al., 2006; Steele et al., 2007; Tamborini et al., 1989; Tang and Sanford, 2005; Tort et al., 2006; Van de Weerd et al., 2001; Zarrinhalam et al., 2012), unfamiliar environment (Alexandrov et al., 2015), short-term monitoring, manual scoring (human error) (Friard and Gamba, 2016; Noldus, 1991), time-consuming analysis, invasive marking (e.g. use of hair dye that might interfere with social behavior) (Sams-Dodd, 1995; Shemesh et al., 2013; Spink et al., 2001; Vatine et al., 1998), slow system performance, ID swapping that has to be corrected manually, no differentiation between animals' IDs (Arakawa et al., 2014), loss of track due to animal disappearing from camera view, no use of environmental enrichment or bedding (Crispim Junior et al., 2012), limited readout (e.g. position in the cage/proximity to detectors but no complex behaviors including following, approaching etc.) (Bains et al., 2016; Catarinucci et al., 2014; Howerton et al., 2012; Lewejohann et al., 2009; Macri et al., 2015). Table 3 is summarizing benefits and limitations of multi-animal tracking approaches.

1.8. Tracking solutions

The first step of automation has been taken by recording behavior experiments on video allowing manual scoring and re-scoring of behaviors “off-line”. Software solution such as Observer XT, Noldus Information Technology or BORIS (Behavioral Observation Research Interactive Software) simplified manual video scoring by digitalizing data output. This allows the observer to press keys coding for different behaviors synchronized with video data (Friard and Gamba, 2016; Noldus, 1991). Automatic video-based tracking has become a prominent tool for behavior observations since it is simple to use and easy to

validate by human observation, especially when tracking is visualized online. Video-based tracking solutions for locomotor behavior and position tracking of a single animal are either commercially available such as Ethovision (Spink et al., 2001) and Viewer (Krueger-Burg et al., 2016), or freely available such as Mousetracker (Tort et al., 2006), OpenControl (Aguilar et al., 2007), Ethowatcher (Crispim Junior et al., 2012), MiceProfiler (de Chaumont et al., 2012), idTracker (Perez-Escudero et al., 2014) and others (Aragão et al., 2011; Jhuang et al., 2010; Zarrinhalam et al., 2012). The majority of video-based tracking solutions is using background subtraction (Maddalena and Petrosino, 2008) to identify moving objects that significantly differ from the background frame (frame of the arena without any animal inside). Therefore, such tracking approaches are limited by the use of bedding material, camera position and lighting conditions (arena illumination, shadow of the animal) contributing to tracking errors. Furthermore, commercial video-based tracking solutions generally do not permit any modifications or extensions of the code to suit user's research purpose (unless additional license key are purchased or the code is modified/fixed by vendor). However, the main challenge for video tracking is the reliable recognition of individuals in a group of animals unless they are visibly labelled (Shemesh et al., 2013; Spink et al., 2001). Though, few tracking algorithms requiring no marking have been described, e.g. Smart Vivarium (Belongie et al., 2005), idTracker (Perez-Escudero et al., 2014), MiceProfiler (de Chaumont et al., 2012).

Further techniques monitoring animal's activity and location in the arena include RFID, IR sensors, and others. Sensor-based tracking systems (Bode et al., 2008; Casadesus et al., 2001; Solberg et al., 2006; Tamborini et al., 1989; Tang and Sanford, 2005; Urbach et al., 2014) detect single photo-beam breaks produced by animal's movement in the arena and are suited for long-term monitoring. However, sensors suffer from low spatial resolution and are insufficient to detect other behaviors like grooming or rearing (though can be measured indirectly by

vertical breaks) or social interactions. Radio-frequency identification (RFID) is using radio waves to communicate between transponder and reader. RFID transponders are small chips implanted subcutaneously providing unique identification suitable for long-term tracking of large groups of animals in the arena. Several commercial RFID solutions such as the IntelliCage (Endo et al., 2011; Galsworthy et al., 2005; Rudenko et al., 2009) and HCA system (Bains et al., 2016) as well as non-commercial solutions (Catarinucci et al., 2014; Howerton et al., 2012; Lewejohann et al., 2009; Macri et al., 2015; Puścian et al., 2016) have been described in the literature. However, limitations of RFID usage imply interference of the magnetic fields of adjacent readers and the inability of low frequency (LF) and high frequency (HF) RFID systems to read multiple tags simultaneously. However, ultra-high frequency (UHF) bandwidth (860–960 MHz) allows multiple and simultaneous tag reading (Catarinucci et al., 2014; Macri et al., 2015). RFID-based tracking approaches can be used to assess different aspects of social behavior (Howerton et al., 2012; Puścian et al., 2016) without providing details about occurring social postures and events.

1.9. Automatic tracking and analysis system developed for PRISM

Monitoring social behavior under ethological relevant conditions is crucial to assess all aspects of social behavior and social deficits in rodent models of psychiatric disorders. As described above, common tracking solutions lack the ability to capture the full spectrum of social behavior in rodents. Nevertheless, few approaches, combining multiple tracking techniques, such as video tracking and depth sensors (Hong et al., 2015), RFID and video tracking (Alexandrov et al., 2015; Weissbrod et al., 2013), and video tracking combined with machine learning (Shemesh et al., 2013) have been reported.

Recently, a novel automatic tracking system has been developed for long-term behavioral observations of group housed mice: RFID-Assisted SocialScan (Peleh et al., manuscript in preparation). By combining video tracking with RFID signals, the system enables constant monitoring of individual mice without using any visible markers. Therefore, mice are implanted (s.c.) with a small glass-coated RFID tags, which are detected by RFID antennas strategically placed inside and underneath the arena (50 cm x 70 cm) (Fig. 1). The software package synchronizes video images with constantly updating RFID signals and assures animals' identity and location at any time and independent of their visibility to the camera view. The social arena design is based on behavioral apparatus described by Shemesh (Shemesh et al., 2013) including two nests, two ramps, food and water supply with the purpose for creating a semi-natural environment (Fig. 1). One of the hallmarks of RFID-assisted SocialScan is the automatic detection of social (approaching, contact, following, withdrawing, and fighting) and non-social events (e.g. rearing, grooming, running, and walking). Each event can flexibly be predefined based on users' needs. Unlike other tracking systems, RFID-assisted SocialScan benefits from its ability to re-match

switched identities automatically and independent of the time point of occlusion. The newly developed tracking software package is a promising tool to be applied to many different preclinical research questions, especially related to complex social behavior in mice.

2. Reverse translation of other measures into preclinical studies with reference to other manuscripts of this issue of NBBR

The second major aim of the preclinical work package in the PRISM project is the reverse translation of neurophysiological EEG measures and functional imaging and the cognitive profiling of mice stratified for high vs. low social withdrawal in the social interaction paradigm described above.

2.1. Sensory processing

An untapped source of potential for translational research is that of sensory processing. It has been a long-held idea that deficits in sensory processing could be providing the common phenotype observed in diagnosable clinical symptoms (James et al., 2011). The majority of sensory processing tasks have developed from the desire to better objectively quantify the amount of information a patient is capable of processing. Deficits in any sensory modality can lead to dramatic differences in responsiveness to treatment, ease of diagnosis and characterization of patient's problem (Polich et al., 1986; Näätänen et al., 2014). A sensory processing task, the auditory steady state response task (ASSR) was developed for just this reason (Campbell et al., 1977). The ASSR characterizes, through electroencephalographic (EEG) measurements, the connectivity and functioning of different populations of auditory neurons (Yokota et al., 2017; Sousa et al., 2016). Deficits herein provide clinical support to hearing deficits, or simple auditory connectivity changes, which could provide evidence of functional brain alterations (Brenner et al., 2009). A further commonly used clinical assessment tool is that of the resting-state EEG to localize brain abnormalities, observe brain connectivity and observe the spectral composition of the generated brain signals (Miraglia et al., 2017). Using ASSR and resting state EEG as examples, it is easy to show how reverse translation can be of great benefit for clinical applications. In order to fully determine what the collected EEG signals indicate in terms of underlying neuronal changes, translational research is necessary. In translational models, rodents are implanted with monochannel or multichannel electrodes on the frontal, parietal and/ or occipital cortex and auditory stimuli are presented as click trains of 0.2 msec clicks at a rate of 10–80 cycles/ sec. By using electrophysiology concomitantly with EEG, it is possible to characterize subpopulations of neurons contributing to each aspect of the resulting EEG signal. This research is impossible in human populations but provide great insight about brain functioning which can be applied to understanding clinical results.

Another common clinical application of sensory processing research is the measurement of mismatch detection through the detection of event-related potentials (ERPs). By measuring the ability for a patient to detect deviance from a norm, much understanding can be reached in terms of understanding the sensory perception of a patient. A good example of this is by the mismatch negativity (MMN) paradigm (Näätänen et al., 1980). When considering patients diagnosed with schizophrenia, the objective observation of their primary auditory detection and their cognitive processing of the perceived sound to determine deviance (mismatch) can be invaluable. This is made possible by the ability to collect both these interacting processes as components in the resulting EEG signal. The deficits common to schizophrenics are well known using this method in clinical settings, with patients eliciting lower MMN amplitudes (Fulham et al., 2014; Sauer et al., 2017). Another patient population where MMN testing routinely is conducted is that of Alzheimer's disease (AD). Those diagnosed with AD show a similar phenotype with also the reduction of MMN amplitude in comparison to healthy controls (Pekkonen et al., 1994). Currently only

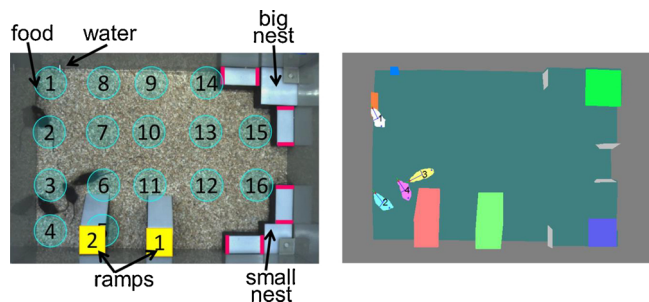


Fig. 1. Automatic RFID-assisted video tracking system. Left: Behavioral arena with 16 RFID antennas (blue), 8 nest antennas (pink), and two ramp antennas (yellow). Right: Illustration of animal's shape detection (each animal is labelled based on its RFID tag). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

auditory paradigms have been applied in clinical situations but there are many possibilities for reverse translation. Other sensory modalities and the possible deficits, lack of deviance detection or lack of sufficient processing, therein could be key for future clinical applications. An example of this is the attempt to develop a rodent visual MMN procedure (Hamm and Yuste, 2016). Head-fixed mice view a striped pattern in two orientations on a monitor while running on a treadmill. The stimuli are presented for 500 msec (1000–1500 msec interval) with a probability of 12.5% for the deviant pattern during multi-electrode recordings in the visual cortex. The deviant versus redundant effect in the peak LFP channel is significantly different with a time course similar to human MMN. By being able to accurately test the primary stimulus and cognitive processing of visual perception, a great step in understanding brain functioning can be made. As this work provides evidence for the ability to detect a mismatch in other sensory modalities, it is not too far to extend this idea to more clinically relevant modalities. An example of this would be the development of an olfactory MMN paradigm. The ability to detect deficits in olfactory processing at an early stage could be an excellent early diagnosis tool for Alzheimer's disease. Alzheimer's disease patients often suffer early loss of smell detection. So far, this has not been a major target of early diagnosis, however, this could be the perfect application of translational sensory processing research. The thorough knowledge gained through animal research could provide the necessary basis for a working model to be applied in the clinic, providing a much-needed early detection tool.

2.2. Attention (5C-CPT)

The neurocognitive domains of attention and cognitive control are highly relevant to deficits observed in both schizophrenia and Alzheimer's disease (AD) (Young et al., 2013, 2017; Perry et al., 2000). In recent years, there has been tremendous interest in developing translational approaches to modelling neurocognitive domains of function and the areas of attention and cognitive control have seen significant progress in the bridging of human and rodent assessments (Insel et al., 2010; Keeler and Robbins, 2011; Cuthbert and Insel, 2013; Cuthbert and Kozak, 2013; Homberg, 2013; Moore et al., 2013; Young and Geyer, 2015). In humans, a number of tasks have been developed to assess the cognitive control of attention such as Go/NoGo tasks, continuous performance tests (CPT), and the Stroop task (Conners, 1985; Smith et al., 2004; MacDonald, 2008; Westerhausen et al., 2011). Go/NoGo tasks allow response inhibition to be assessed, while the Stroop task permits performance monitoring to be assessed. On the other hand, CPT tests allow for an especially rich assessment of response selection, response inhibition, performance monitoring, and goal maintenance and updating to be conducted. Cross-species approaches have been developed to probe many of the aforementioned cognitive control processes such as the sustained attention task (SAT), the 5 choice serial reaction time task (5CSRTT), and the 5 choice continuous performance test (5C-CPT) (McGaughy and Sarter, 1995; Robbins, 2002; Humby et al., 2005; Young et al., 2009; Barnes et al., 2012; Cope et al., 2016a, b). The SAT and 5CSRTT both allow for response selection/suppression, sustained attention, and impulsivity to be measured but are limited in their ability to test for response inhibition. The 5C-CPT overcomes this limitation by including both target and non-target stimuli that allow response selection/suppression as well as response inhibition to also be rigorously assessed, respectively.

The rodent 5C-CPT involves the use of an apparatus that allows lights to be delivered as stimuli in 5 spatially-adjacent apertures. On target trials, a single light is illuminated and rodents are trained to nosepoke into the aperture for a reward to signal a response. On non-target trials, all 5 lights are simultaneously illuminated and animals must withhold their response. The human 5C-CPT is a translated version of the rodent 5C-CPT and utilizes a very similar experimental task design. Like the rodent 5C-CPT, lights illuminate on target trials in one

of 5 spatial locations and subjects are required to signal a response by utilizing a joystick to move it to the illuminated location. On non-target trials, all 5 lights are illuminated and subjects must withhold a response on the joystick.

While further work needs to be done to clarify exact neural substrates mediating various aspects of performance on the 5C-CPT, fMRI studies utilizing the human 5C-CPT suggest that frontostriatal and parietal networks appear to play an important role (Eyler et al., 2011). Given the significant neocortical deficits characteristic of both schizophrenia and AD, one would expect CPT tests to be robust to the cognitive deficits that accompany such disease states. Importantly, the human 5C-CPT is clinically sensitive to the deficits observed in patients with schizophrenia and the brain activations elicited in this task are consistent with other types of CPTs (Young et al., 2013, 2017; McKenna et al., 2013). Performance by AD patients in CPTs also demonstrates attentional disruption early in disease and suggests that tests such as the 5C-CPT could be valuable for highlighting both similarities as well as differences between schizophrenia and AD. Recently, the human 5C-CPT has been extended as a translational paradigm to include EEG-based assessments for neurophysiologically characterizing schizophrenics versus healthy controls. (Buckner and Krienen, 2013) These findings demonstrate that schizophrenics have decreased N₂ (to target and non-target stimuli) and P₃ (to non-target stimuli) amplitudes relating to impairments in response selection and action. The possibility of utilizing the 5C-CPT as a platform to generate functional EEG/ERP biomarkers across diseases promises to greatly expand its value for patient selection and phase II drug development.

While CPT tasks such as the 5C-CPT offer much potential in terms of human patient endophenotyping and cross-species translation, a number of important caveats must be kept in mind.

One important caveat relates to species differences. In particular, similarities between rodent and human frontal cortex are minimal and rodents have no clear correlate of human posterior cingulate cortex/area 23 (Buckner and Krienen, 2013; Vogt et al., 2004). Furthermore, while they may have some subsystems of large-scale human functional networks (e.g. ventral default mode network (DMN) subsystem), rodents appear to lack the complete large-scale functional networks of humans (e.g. DMN) thought to enable cognitive processing (Stafford et al., 2014). These findings taken together suggest that the same fronto-parietal networks that are implicated as central to human 5C-CPT performance may not be at play in the rodent brain. Furthermore, if fronto-parietal neural substrates do exist in rodents, the neural substrates mediating rodent performance on the 5C-CPT as well as the brain activations (as measured by EEG or fMRI, for instance) associated with various aspects of task performance may not be subject to the same cognitive regulation as in humans or may not signify the processing of similar content. The implications with regard to disease mechanism and therapy are profound and much further work is needed to fully understand the translational capabilities and limitations of these tasks (Young et al., 2009).

A second important caveat to bear in mind is that, depending upon the disease in question, impairments in attentional function could either be primary or arise secondary to some other remote insult (Perry et al., 2000). Thus, the nature of attentional impairments could markedly differ between diseases. For instance, there is early and significant medial temporal lobe (MTL) pathology that is characteristic of AD that appears to give rise to an amnesic phase of disease relatively devoid of significant attentional impairments. The MTL memory system is extensively connected with fronto-parietal systems that appear to be key to CPT performance. As AD pathology progresses, it is possible that higher cognitive fronto-parietal networks become indirectly compromised through a deteriorating MTL memory system. Schizophrenics on the other hand have profound disinhibition that occurs throughout both MTL and prefrontal cortex (PFC) (Heckers and Konradi, 2015; Gonzales-Burgos et al., 2015; Lewis and Glausier, 2016). Such changes could affect both primary and secondary changes that compromise

fronto-parietal systems, leading to potentially overlapping, yet distinct, behavioral and neurophysiological phenotypes. A combination of behavioral and neurophysiological assessments that are sensitive to different domains of attention and memory is warranted to best establish areas of overlap and differentiation between diseases.

2.3. Working memory (odor span task)

Working memory is a neurocognitive domain significantly impacted in both AD and schizophrenia (Van Geldorp et al., 2015; Goldman-Rakic, 1994; Stopford et al., 2012). The selection of the odor span task to probe olfactory memory builds on a large literature, some of which is reviewed below, demonstrating that in AD and schizophrenia patients, olfactory memory is significantly compromised. By providing a controlled source of non-spatial input (smell) into key frontal and temporal regions impacted by schizophrenia and AD pathology, potentially translational cross-species approaches can be developed and implemented for use in patient stratification and drug development.

Deficits in olfactory recognition memory are evident early in schizophrenia, mild cognitive impairment (MCI) and AD (Kopala et al., 1993; Wu et al., 1993; Goudsmit et al., 2003; Kästner et al., 2013; Gill et al., 2014; Devanand et al., 2000; Larsson et al., 1999; Gilbert and Murphy, 2004; Roberts et al., 2016). The involvement of olfactory deficits early in disease and the ability to cheaply and quickly utilize olfactory probes as a potential early disease biomarker for schizophrenia or AD makes olfactory assessments extremely attractive. To this end, tests such as the brief smell identification test (B-SIT) and University of Pennsylvania Smell Identification Test (UPSIT) have been developed and utilized in large studies of schizophrenia, MCI, and AD cohorts (Doty et al., 1996, 1984). Utilizing the UPSIT, Kästner et al. demonstrated that schizophrenic patients displayed significant deficits in odor naming (active memory retrieval) and interpretation (attribute assignment) and that these deficits were primarily associated with compromised cognition and positive symptom severity, respectively (Kästner et al., 2013). A number of studies have documented olfactory impairments in association with MCI and with the progression from MCI to dementia (Larsson et al., 1999; Graves et al., 1999; Swan and Carmelli, 2002; Talbert et al., 2005; Kjelvik et al., 2007; Wilson et al., 2007a, 2007b; Devanand et al., 2008, 2015; Stanciu et al., 2014). A separate study by Roberts et al. followed 1630 elderly participants between 2004 and 2014 and assessed olfactory function using the B-SIT every 15 months (Robert et al., 2016). The main findings were that decreased olfactory identification was significantly associated with an increased risk of developing amnesic mild cognitive impairment (aMCI) and that the B-SIT score was predictive of progression from aMCI to AD.

Key neural substrates underlying olfactory function can be localized to frontal and temporal brain regions, particularly the piriform cortex, entorhinal cortex (EC), hippocampus, amygdala, and orbitofrontal cortex (Wilson et al., 2007a, 2007b). Given the early atrophy and neurofibrillary tangle deposition in the entorhinal cortex in AD, it is perhaps unsurprising that deficits in the EC specifically and MTL memory system generally would yield early olfactory deficits in aMCI and AD (Khan et al., 2014). With regard to AD, olfactory impairment has been associated with amyloid beta plaques and neurofibrillary tangle pathology in the olfactory bulb, hippocampus, and entorhinal cortex (Wilson et al., 2007a, 2007b). Furthermore, neocortical and hippocampal disinhibition is hallmark of schizophrenia, which results in disrupted functional connectivity in the aforementioned areas that contribute to the olfactory system (Benarroch, 2010; Turetsky et al., 2003, 2009; Uhlhaas and Singer, 2010; Heckers and Konradi, 2015; Gonzales-Burgos et al., 2015; Lewis and Glausier, 2016).

The rodent odor span task is a delayed nonmatching to sample task that was originally developed to assess olfactory working memory first in rats and then later in mice (Dudchenko et al., 2000; Young et al., 2007). In this task, rodents are placed in an arena and must dig in

differently scented pots to obtain rewards. The rodents begin with 1 pot present in the arena, are removed, and then presented with two pots in different locations, one of which is the original scent and a newly scented one. The rodents must then pick then newly scented pot to dig in to obtain the reward. This continues with a new pot being added on each trial until the rodent digs in a previously visited pot. Amazingly, complete hippocampal lesions had no effect on rodent odor span memory, even up to spans of 24 distinct odors. This stands in stark contrast to findings in human amnesics with damage limited to the hippocampus, who are significantly impaired in odor recognition span tests (Levy et al., 2003). These discrepant findings suggest that rodents may be able to perform the task entirely within olfactory working memory supported by the PFC and other components of the olfactory memory system such as the entorhinal cortex. In support of this notion, medial prefrontal cortex (mPFC) inactivation profoundly impairs odor recognition span performance in rats, but in humans the role of the PFC in span tasks is somewhat controversial (Davies et al., 2013; D'Esposito and Postle, 1999; Bor et al., 2006). Further work is needed to resolve the similarities and differences of the underlying neural substrates supporting cross-species odor recognition span performance. While data from large human trials in schizophrenia, aMCI, and AD is extremely encouraging and suggests olfactory recognition tests could be highly useful for patient stratification and drug development, caution must be taken in translating findings across species when rodents may rely upon slightly different systems to perform these tasks.

3. Summary

A preclinical test battery has been put together for reverse translation of an established human test battery for exploring the correlation of social withdrawal and cognitive impairment. Elements of the clinical and preclinical test batteries have been selected for addressing the same underlying physiological parameters (e.g. the EEG tasks) and for addressing comparable social and cognitive domains such as working memory or special memory (Table 4). Details of the clinical test battery and the rational for their selection have been described in other manuscripts of this issue.

Careful alignment of the clinical and preclinical tasks is a prerequisite for reverse translating the multi-dimensional approach of PRISM. For an experimental, preclinical approach to study the complex connection between social withdrawal and cognitive impairment and to evaluate potential genes and mechanisms involved in regulating this connection, standard dyadic rodent tests were not suitable since they do not reflect the human situation of living in a society. Identification of a preclinical setup, which allows for long-term monitoring of social interaction of a group of mice was a key component for the PRISM approach. However, evaluation of the current literature, summarized in this review, revealed that a setup for long-term monitoring of individual animals in a group of mice living in a large social arena without visibly marking the animals has not been described yet. The PRISM consortium

Table 4
Aligned clinical and pre-clinical test batteries of social and cognitive domains.

Human task	Mouse equivalent
Smartphone application	Social group behaviour
Social functioning scale	Social group behaviour
Social incentive delay – MRI: 15 min. MID, incl. motivation – (outside the scanner),	Social conditioned place preference
Resting state eyes open and closed	Three chamber task
MMN auditory (passive)	Resting state EEG.
Steady-state auditory-evoked potential	MMN auditory
	Steady-state auditory-evoked potentials
N-back – with fMRI	Odour span task
Arena task- with fMRI	Morris water maze
Continuous performance task	5C-CPT

provided now the framework and required expertise for developing and establishing such a setup for studying mouse social behavior in a large, semi-natural arena without being influenced by the experimenter. This social mouse behavior task reverse translates the BeHAPP app and is the last component of a fully reverse translated test battery for experimentally addressing the findings of the human deep phenotyping studies. The test battery described here will help to elucidate the RDoC symptom domain cognitive systems and the construct social communication by providing the tools for experimentally bridging the behavioral dimensions and physiology to brain circuits and genes. This approach consistently implements the RDoC matrix and will help to identify and evaluate new therapeutic concepts for the treatment of psychiatric diseases.

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